Etiology and Prevention of Cervical Adenocarcinomas

Allan Hildesheim, Amy Berrington de González

Adenocarcinomas of the uterine cervix (ACs) constitute a relatively rare histologic form of cervical cancer. However, while rates of the more common squamous cell carcinomas of the cervix (SCC) have shown consistent declines in incidence over time in countries where effective cytological screening programs exist, rates of AC have increased over the same period *(1–3)*. This has led to an increase in the proportion of cervical cancers attributable to AC in many countries. In the United States, ACs now make up more than 20% of all cervical cancer cases diagnosed each year *(4)*.

The underlying reasons for the increases observed for AC are not well understood. They are likely due to a complex interplay between temporal changes in exposures that predispose to the development of AC and changes in cervical cancer screening practices *(1)*. Changes in screening practices and their likely impact on AC rates are in themselves difficult to understand because they include changes that are likely to have countervailing effects on disease rates. For example, increased awareness of AC, improved diagnostic classification of these conditions, and improvements in cervical sampling devices and slide preparation methods might initially result in increased detection of invasive AC. These improvements would also lead to increased detection of AC at an earlier—in situ—state, which would subsequently lead to decreases in overall rates of invasive AC. Unlike the situation with SCC, however, this predicted long-term impact of improved screening on AC rates might be muted by limitations resultant from the difficulty of detecting AC, which often arise deep in the endocervical canal, in areas that despite the improvements in screening alluded to above are still not easily sampled during routine screening.

In this issue of the Journal, Castellsagué and colleagues report findings from a multicenter study of AC *(5)*. The results have important implications for our understanding of both the causes and possible prevention of AC. Each of these aspects is discussed below.

Etiology

Results from the study by Castellsagué et al. clearly reinforce evidence for a strong link between HPV and AC, similar to that which has been shown for SCC. Further, their report demonstrates that the HPV types observed in AC and SCC overlap and that HPV 16 is the most common HPV type seen for both histologic types. The report also confirms that a higher proportion of AC than SCC contain HPV 18 infection, particularly in younger women, among whom nearly half of AC cases were positive for HPV 18. Together, HPV 16 and 18 accounted for approximately 85% of AC cases, compared with approximately 70% of SCC cases *(6)*.

Given that AC and SCC share HPV at their central etiologic agent, it is not surprising that these two histologic types of cervical cancer were also found to share behavioral cofactors that mediate risk of HPV exposure, including number of partners, age at initiation of sexual activity, and herpes simplex virus 2 seropositivity. Apart from sexual behavior cofactors, evaluation of additional cofactors for AC and SCC might shed light on differences in the etiologic profile of these two diseases. Cigarette smoking is the clearest example of a risk factor with divergent effects on risk of SCC and AC. Although smoking has been established as a risk factor for SCC *(7)*, Castellsagué et al. found that it was not associated with risk of AC, and other studies *(8,9)* have found an inverse association. It is interesting that endometrial cancer, which mirrors cervical adenocarcinomas in its largely glandular histology, is also inversely associated with cigarette smoking. Thus, AC might share HPV and sexual behavior risk factors in common with SCC but other risk factors in common with endometrial adenocarcinomas.

Because many of the risk factors that have been identified for endometrial adenocarcinoma (including, potentially, smoking) have a hormonal basis *(10)*, one might speculate that hormonal risk factors are important predictors of AC risk. Oral contraceptive use and parity are two cofactors evaluated by Castellsagué et al. that might be associated with disease due to hormonal influences. Evaluation of these factors in the present and previous studies presents a less than clear picture of similarities and differences in hormonal influences on risk of SCC and AC, however. For example, long-term use of oral contraceptives is associated with an increased risk of AC, SCC, and endometrial adenocarcinomas *(10,11)*, whereas parity, which is consistently associated with risk of SCC *(12)*, has a more muted association with AC and is inversely associated with endometrial adenocarcinomas *(10)*. Future efforts to dissect differences in the risk factor profile for SCC and AC could benefit from a focus on hormonal risk factors.

Prevention

Castellsagué et al.'s results also have important implications for cervical cancer prevention efforts. First, their data indicate that women with a history of Pap smear screening have a reduced risk of developing AC. Although Pap smear screening has not historically been effective at reducing rates of AC, and interpretation of Pap smear efficacy data from case–control studies is complicated by the potential for confounding and detection biases, it is nevertheless reassuring that, in the present

Affiliations of authors: Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD (AH); Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD (ABdG).

Correspondence to: Allan Hildesheim, PhD, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd., Rm. 7062, MSC 7234, Rockville, MD 20852 (e-mail: hildesha@mail.nih.gov).

DOI: 10.1093/jnci/djj098

study, a reduced disease risk was observed among screened women. Given the improvements in Pap smear programs in recent years, one might expect the increase in the rates of detection of in situ AC to translate into a decrease in rates of invasive AC in future years. Clearly, women should continue to be counseled to avail themselves of cervical cancer screening programs.

HPV DNA testing has begun to be incorporated into screening programs, either as an adjunct to the Pap smear or as primary screening for women aged more than 30 years *(13)*. The confirmation by Castellsagué et al. that the HPV types detected in AC are the same as those detected in SCC suggest that screening for HPV might have a beneficial impact on both histologic subtypes of cervical cancer. In fact, to the extent that HPV infections that lead to cancer are detectable throughout the cervix (i.e., HPV infection affects the entire "field")—whereas AC lesions are sometimes limited to the upper levels of the endocervical canal, where they can be missed by Pap smear sampling—HPV testing may prove to be a useful tool for improving the detection of AC.

Finally, prophylactic HPV vaccines have recently been shown to be highly effective at the prevention of persistent HPV infection for at least 2–3 years *(14,15)*. The first-generation HPV vaccines currently being tested in large-scale efficacy trials are expected to provide protection against the two most common HPV types observed in SCC: types 16 and 18. Given the data by Castellsagué et al., indicating that the proportion of AC cases attributable to HPV 16/18 (~85%) is higher than that reported previously for SCC (~70%) *(6)*, one might predict that HPV 16/18 vaccination will have a greater proportional impact on rates of AC than on those of SCC.

Despite increases in AC rates in recent decades, it would not be unrealistic to expect rates of AC to drop in future years, as screening continues to be improved, HPV testing is incorporated into (or in some instances replaces) Pap smear screening programs, and prophylactic HPV 16/18 vaccines become available for broad use. The new challenge facing policymakers and the public health community at large is to use the various tools now at our disposal to reduce disease burden associated with SCC and AC in the broadest, most rational, and cost-effective manner.

References

(1) Wang SS, Sherman ME, Hildesheim A, Lacey JV Jr, Devesa S. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976–2000. Cancer 2004;100:1035–44.

(2) Bray F, Carstensen B, Moller H, Zappa M, Zakelj MP, Lawrence G, et al. Incidence trends of adenocarcinoma of the cervix in 13 European countries. Cancer Epidemiol Biomarkers Prev 2005;14:2191–9.

(3) Bray F, Loos AH, McCarron P, Weiderpass E, Arbyn M, Moller H, et al. Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. Cancer Epidemiol Biomarkers Prev 2005;14:677–86.

(4) Smith HO, Tiffany MF, Qualls CR, Key CR. The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States—a 24-year population-based study. Gynecol Oncol 2000;78:97–105.

(5) Castellsagué X, Díaz M, de Sanjosé S, Muñoz N, Herrero R, Francheschi S, et al. Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. J Natl Cancer Inst 2006;98:303–15.

(6) Munoz N, Bosch FX, De Sanjose S, Herrero R, Castellsague X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 2003;348:518–27.

(7) International Collaboration of Epidemiological Studies of Cervical Cancer. Carcinoma of the cervix and tobacco smoking: Collaborative reanalysis of individual data on 13541 women with carcinoma of the cervix and 23017 women without carcinoma of the cervix from 23 epidemiological studies. Int J Cancer 2006;118:1481–95.

(8) Berrington de Gonzalez A, Sweetland S, Green J. Comparison of risk factors for squamous cell and adenocarcinomas of the cervix: a meta-analysis. Br J Cancer 2004;90:1787–91.

(9) Lacey JV Jr, Frisch M, Brinton LA, Abbas FM, Barnes WA, Gravitt PE, et al. Associations between smoking and adenocarcinomas and squamous cell carcinomas of the uterine cervix (United States). Cancer Causes Control 2001;12:153–61.

(10) Grady D, Ernster VL. Endometrial cancer. In: Schottenfeld D, Fraumeni JF Jr, editors. Cancer epidemiology and prevention. 2nd ed. Oxford (UK): Oxford University Press; 1996. p. 1058–89.

(11) Smith JS, Green J, Berrington de Gonzalez A, Appleby P, Peto J, Plummer M, et al. Cervical cancer and use of hormonal contraceptives: a systematic review. Lancet 2003;361:1159–67.

(12) Munoz N, Franceschi S, Bosetti C, Moreno V, Herrero R, Smith JS, et al. Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. Lancet 2002;359:1093–101.

(13) Wright TC Jr, Schiffman M, Solomon D, Cox JT, Garcia F, Goldie S, et al. Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. Obstet Gynecol 2004;103:304–9.

(14) Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. Lancet 2004;364:1757–65.

(15) Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol 2005;6:271–8.